UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,764	04/27/2000	Hans Jakob Flodgaard	5694.200-US	2707

7590 12/21/2001

Miriam Kelly
Novo Nordisk of North America Inc
405 Lexington Avenue
Suite 6400
New York, NY 10017

EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/21/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,764	FLODGAARD ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11 and 15-52* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 15-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/16/01 (Paper No. 11), is acknowledged.
Claims 1-6 and 12-14 have been cancelled.
Claims 43-52 have been added.
Claims 7-11 and 15-52 are pending.

Claims 7-11 and 15-42 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 43-52 *are under consideration in the instant application.*

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 10/16/01 (Paper No. 11). The rejections of record can be found in the previous Office Action (Paper No. 8).

It is noted that New Grounds of Rejection are set forth herein.

3. Applicant's cancellation of Claims 1-6 and 12-14 have obviated the previous objections and rejections with respect to Claims 1-6 and 12-14.

4. Priority: Neither provisional application 60/12,748 (4/29/99) nor 60/157,384 (10/1/99) appear to provide adequate written support for an antibody to the specific epitope of bradykinin or for a human antibody; thus claims 46 and 47 are considered to have the priority date of the instant application (4/27/00).

Applicant is invited to point to clear support for the claimed subject matter in each provisional application; if Applicant disagrees with the Examiner's analysis.

5. Applicant's indication that the Abstracts present on the IDS filed 11/9/00 are the same source as the full references also listed on the IDS is noted. Since the Abstracts represent duplicate information, they will remain crossed off the IDS.

6. Claims 43-44 and 46-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 43-44 and 46-52 are indefinite in that they only describe the compositions of interest by the arbitrary protein name "heparin binding proteins (HBP)". While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein. For example, others in the field may isolate the same protein and give such an entirely different name (e.g., see Rasmussen et al. FEBS Lett. 390:109-112 1996). In addition, other proteins are known in the art that also bind to heparin and therefore constitute "heparin binding proteins", e.g., collagen. Applicant should particularly point out and distinctly claim the HBP by claiming characteristics associated with the protein (e.g. a SEQ ID NO:, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and of what the composition is made.

Applicant's arguments, filed 10/16/01, have been full considered, but have not been found convincing, essential for the reasons of record in Paper No. 9.

Applicant argues that the functional properties recited in the newly added claims which replaced cancelled claims 1-6 and 12-14, in conjunction with the disclosure at page 11, lines 11-19 renders the term "heparin binding protein" definite.

However, newly added claims 43-44 and 46-52 still do not set forth any structural characteristic of the protein. And although the specification on page 11 indicates that HBP can be a polypeptide having the structure of SEQ ID NO:1, the specification also indicates on pages 11-12 also indicate that "homologous polypeptides" are encompassed by this term, and that these "homologous polypeptides" can have insertion or deletion of one or more amino acid residues, *as well as the substitution of one or more amino acid residues*. Thus the specification does not provide a limiting description of the structure of a heparin binding protein.

The rejection of record is therefore maintained as applied to newly added claims 43-44 and 46-52.

B) Claims 48-51 each recite "the HBP antagonist". However, there is insufficient antecedent basis for this limitation in the claims because independent claim 43 from which these claims depend does not recite "an HBP antagonist". Applicant should amend the claims to recite -- the anti-heparin binding protein antibody --.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

7. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim recites an anti-heparin binding protein (HBP) antibody that binds to an epitope binds of HBP which interacts with kininogen.

While Applicant's disclosure appears to support a role for HBP in the release of bradykinin from H-kininogen after cleavage by kallikrein (e.g., the Examples on pages 44-48 of the specification), the disclosure does not appear to enable the actual binding of an epitope of HBP to kininogen, and therefore does not appear to enable an antibody to the proposed epitope of HBP.

As previously noted, the state of the art clearly recognizes a role for HBP in inflammation (e.g. reviewed in Pereira J. Leukocyte Biol. 57:805-812, 1995). For instance, Pereira teaches that the protein CAP37, which as noted supra is the same protein as the HBP of the instant invention, is involved in inflammation by virtue of multiple functions: binding of endotoxin (LPS/lipid A), direct microbicidal activity, and the recruitment of cells to the inflammatory site (see entire document, especially "Discussion" on page 810). Applicant provides data supporting a role for HBP in mediation of inflammation, as assessed primarily by monitoring changes in endothelial cell (EC) permeability.

However, although Applicant provides evidence that blocking HBP (by binding to aprotinin) or blocking various steps in the direct activation of bradykinin inhibits the HBP-induced increase in EC permeability; it is unpredictable as to whether HBP and kininogen directly interact (i.e., that an epitope of HBP specifically binds kininogen), or whether intermediaries exist that mediate the observed effect. In the absence of objective evidence or working examples indicating that an epitope on HBP specifically binds kininogen; the skilled artisan would not reasonably predict that an antibody that specifically binds to an epitope of HBP, wherein said epitope binds kininogen, could be used to as an HBP antagonist in the prevention or treatment of any disorder. Before the skilled artisan would have a reasonable expectation of successfully producing a monoclonal antibody to the epitope; the skilled artisan would first have to ascertain whether or not an HBP epitope that binds kininogen exists. Thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant has asserted in the Remarks filed 10/16/01 that because independent claim 43 is enabled, the dependent claims are also enabled.

However, as noted supra dependent claim 47 introduces a limitation with respect to the epitope recognized by the anti-HBP antibody that does not appear to have enabling support in the specification as filed. The Examiner acknowledges that an antagonist antibody that binds HBP does appear to inhibit the effects of bradykinin; however, whether or not this effect involves the direct interaction of HBP and kininogen does not appear to have been established. Applicant is invited to provide objective evidence that the instant epitope exists (i.e., objective evidence that HBP and kininogen directly interact) to obviate this rejection.

The rejection of record in Paper No. 9 is maintained as it applies to instant claim 47.

8. Claims 43-44 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Oppenhelm et al. (US Pat. No. 5,837,247, of record, see entire document), as evidenced by Rasmussen et al. (FEBS Lett. 390:109-112 1996, of record, see entire document).

Oppenhelm et al. teach a method for reducing or inhibiting an inflammatory disorder in a subject comprising administering an antagonist of CAP37/HBP (see entire document; e.g., column 2, especially lines 57-67); wherein the antagonist is a polyclonal or monoclonal antibody to CAP37/HBP (e.g., columns 9-10, especially bridging paragraph) and wherein the subject is human (e.g., column 9).

Systemic inflammatory response syndrome encompasses multiple inflammatory disorders; thus the claim is anticipated (see MPEP 2131.02).

CAP37 and HBP are the same protein, as evidenced by Rasmussen et al. (e.g., "Introduction"), and would therefore inherently possess at least about 80% identity to SEQ ID NO:1.

Administration of the same compound (an anti-HBP antibody) would inherently result in decrease in bradykinin release and the downstream effect of attenuation of alterations in endothelial cell permeability in a mammal, since the functional properties of the compound are inherent. Applicant is reminded that when a claim recites using an old composition or structure (e.g. an HBP-specific antibody) and the use is directed to a result or property of that composition or structure (e.g., effective to decrease release of bradykinin), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant is further reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the inherent decreased release of bradykinin in response to administering an antibody to HBP. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

Finally, no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitation of decreasing release of bradykinin would be an inherent property of the referenced anti-CAP37/HBP antibody.

9. Claims 43-46 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oppenhelm et al. (US Pat. No. 5,837,247, of record) as evidenced by Rasmussen et al. (FEBS Lett. 390:109-112 1996, of record); in view of Grunfield et al. (US Pat No. 5,660,826, of record).

The claims are drawn to dosages of administration of an HBP/CAP37 antagonist wherein the antagonist is an antibody, as well as to a human antibody.

Oppenhelm et al. as evidenced by Rasmussen et al. have been discussed supra.

Oppenhelm et al. do not explicitly teach the dosage of administration of the antibody inhibitor of HBP.

Grunfield et al. teach and claim a method comprising administering to a patient suffering from risk of systemic inflammatory response syndrome an effective amount of an antibody inhibitor wherein the antibody inhibitor is administered in the pharmaceutically effective amount of 1μg/kg to 10mg/kg (see entire document, especially claims 1 and 2). Grunfield et al. also teach that the dose is subject to a great deal of therapeutic discretion, and that higher doses may be needed (e.g., column 4, especially lines 23-37).

Given the teachings of Grunfield et al. with respect to dosages of administering antibodies for treating systemic inflammatory response syndrome conditions such as shock; it would have been obvious to the ordinary artisan at the time the invention was made to utilize similar dosages of antibodies to HBP, especially since the therapeutic use of anti-HBP antibodies taught by Oppenhelm et al. is for inhibiting inflammation. The ordinary artisan would have been motivated to utilize these similar dosages in light of the similarities of the therapeutic modality and the conditions treated. In addition, given these similarities, the ordinary artisan would have had a reasonable expectation that the effective dose of the antibody antagonist of HBP was similar to or encompassed by the range taught by Grunfield et al. Finally, the ordinary artisan would have been motivated to formulate the antibody composition in an amount of from about 10 mg to 1g per unit dosage in order to provide sufficient quantities of the antibody preparation in a reasonably compact dosing. Preparation of human monoclonal antibodies, either by phage display or isolation from mice bearing human antibody genes, was a well known alternative means of producing antibodies at the time the invention was made which was art recognized to produce antibodies that were highly desirable for administration to humans. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim allowed

11. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
December 20, 2001

PHILLIP GAMBEL, PH D
PRIMARY EXAMINER
TECH CENTER 1600
12/20/01